35 Clinical Implications of the Role of ^{18}FDG-PET/CT in Malignant Lymphomas

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35.1 Introduction

PET/CT has a key role in final response assessment after chemotherapy in several types of malignant lymphomas, as well as in baseline staging and interim (mid-treatment) evaluation. Its application is widely established in Hodgkin lymphoma (HL) and aggressive B-cell lymphomas, including diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMLBCL) and other related subtypes. Its role in follicular lymphomas, mantle cell lymphoma (MCL), "nodal" T-cell lymphomas and Burkitt lymphoma is less well established, while it is much more controversial in other low-grade lymphomas and primary extranodal lymphomas other than DLBCL.

35.2 PET/CT in Initial Staging

The rationale of using FDG-PET in the initial staging of lymphomas is based on its improved accuracy in determining disease extend, as compared to conventional imaging [1]. FDG-PET is more sensitive than CT, mainly because it can detect disease in normal-sized lymph nodes or facilitate the evaluation of extranodal disease [1, 2]. PET has been reported to change disease stage in up to 40–59 % of the patients when compared to CT and alter therapeutic strategy in 14–23 % of adults and children suffering from HL or non-Hodgkin lymphomas (NHL) [1–3], but these are "global" figures, which may not be applicable in every specific lymphoma subtype.

35.2.1 Classification of Lymphomas According to FDG Avidity

Various lymphoma subtypes are not equally FDG-avid and this mainly depends on their histology and biologic characteristics. "Routinely FDG-avid lymphomas" include HL, DLBCL and other aggressive B-cell lymphomas, Burkitt lymphoma, follicular and MCL and the aggressive T-cell lymphomas (mainly the "nodal" types, such as peripheral T-cell, anaplastic large cell, and angioimmunoblastic lymphoma as well as extranodal NK/T-cell lymphomas), since they are almost invariably 18-FDG avid (>95–100 % of the cases) [2, 4–6]. In contrast, other indolent lymphomas are "variably 18-FDG-avid" or even not at all. Thus, several forms of extranodal lymphomas, including MALT and cutaneous B- and T-cell lymphomas, small lymphocytic, splenic marginal zone lymphoma as well as some rare lymphoma subtypes may not be satisfactorily evaluated by PET/CT.

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35.2.2 Role of PET in the Initial Staging of Lymphomas

Among the above named routinely FDG-avid lymphomas, baseline PET/CT for initial staging is not considered mandatory; however, it is strongly recommended as it can facilitate the interpretation of post-treatment PET/CT in HL and DLBCL, including PMLBCL [6] (Figs. 35.1a, 35.2a, 35.3a, 35.4a, 35.5a, and 35.7a). Interestingly, the current trend is to include baseline PET/CT as a mandatory imaging study in the near future [7]. In HL, where the number and density of Hodgkin-Reed-Sternberg cells in the tumor vary, FDG uptake occurs mainly by the inflammatory tumor microenvironment, while in NHL FDG uptake occurs mostly from the malignant cells. In HL, PET/CT identifies 25–30 % more lesions and leads to upstaging in 15–25 % of patients compared to conventional staging. Conversely, up to 10 % of the patients can be downstaged [1]. Such changes might lead to major treatment modification in half of these cases. In a more common scenario, the identification of more disease sites may affect irradiation fields, even in the absence of stage shift. However, current treatment approaches are based on conventional staging. Thus, it is not clear whether stage shift according to PET/CT should guide treatment decisions in HL. The situation is similar in DLBCL, the commonest form of aggressive B-cell lymphoma, but the effect on treatment decisions with standard Rituximab-based chemoimmunotherapy may be less important. The effect on potential irradiation fields may not be so relevant in DLBCL, since radiotherapy is not routinely applied in the majority of patients in many centers.

In the other routinely FDG-avid lymphomas, especially follicular lymphomas and MCL, PET/CT is considered mandatory only if PET-based criteria are going to be used for response evaluation [6]. However, this is not the case in the everyday practice and is mainly recommended within the context of clinical trials. Baseline PET evaluation is also not recommended in lymphoma subtypes which are not routinely FDG-avid [6] (Fig. 35.6).

In malignant lymphomas, the degree of FDG uptake has been proposed to correlate with tumor grade, proliferative activity and aggressiveness, and to be of prognostic value [2]. Studies using semiquantitative measurements based on SUVmax suggest that SUVmax >10 is usually seen in aggressive or transformed indolent lymphomas [2]. This may contribute to the identification and histologic confirmation of transformed disease in patients with known indolent lymphomas.

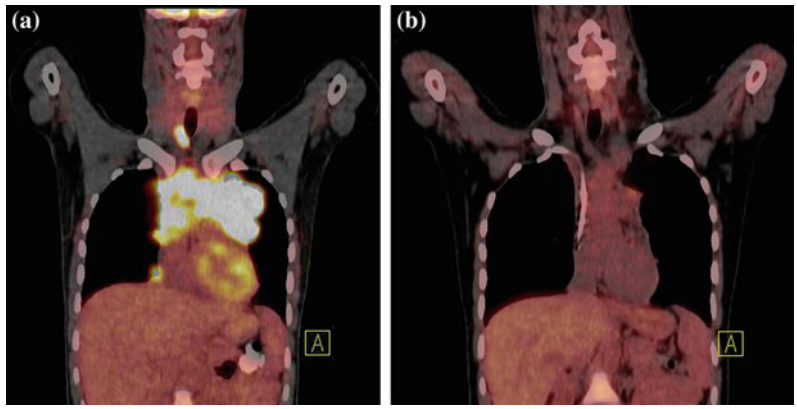

Fig. 35.1 **a** Baseline staging in a patient with Hodgkin lymphoma. Intense FDG uptake is shown in a bulky mediastinal mass. *Right* cervical and *right* epiphrenic nodal involvement is also shown. **b** Post chemotherapy evaluation revealed a residual madiastinal abnormality with FDG uptake higher than the mediastinal blood pool, which is interpreted as positive, i.e., suggestive of residual active disease

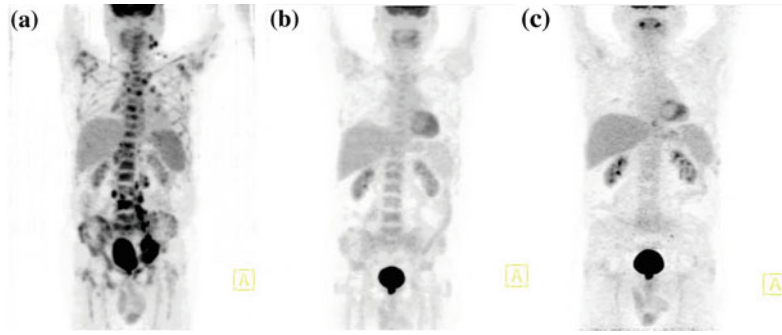

Fig. 35.2 **a** Baseline staging in a patient with diffuse large B-cell lymphoma. Disseminated lymphadenopathy including a left pelvic mass and multiple focal osseous/bone marrow lesions suggestive of bone marrow involvement are consistent with stage IV disease. **b** Interim PET after two cycles of R-CHOP is completely negative. **c** Post R-CHOP evaluation is also negative, as correctly predicted by the negative interim examination

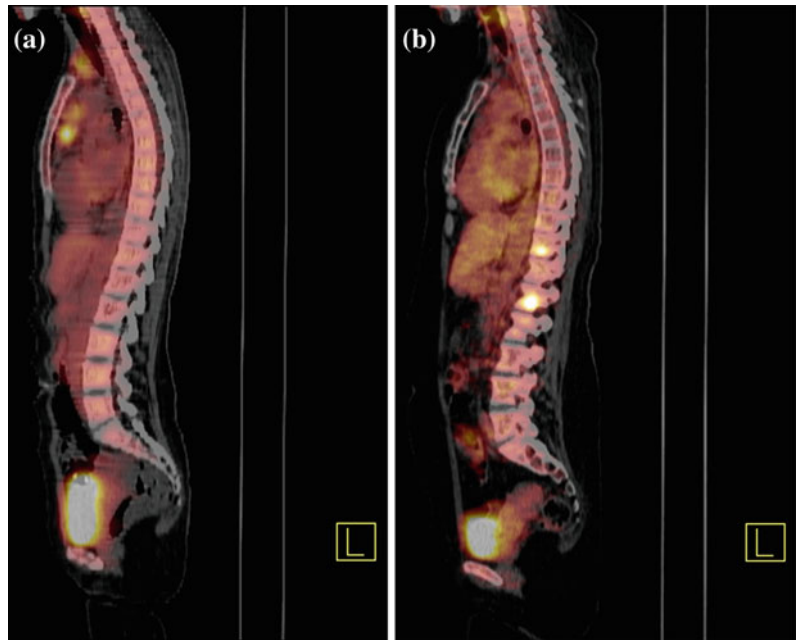

Fig. 35.3 **a** Baseline staging in a patient with Hodgkin lymphoma, indicating cervical and mediastinal involvement. Conventional staging had revealed mildly enlarged paraortic nodes, which were not demonstrable by PET/CT. Thus, the patient was downstaged from clinical stage IIIA to PET-stage IIA. **b** PET/CT at the time of relapse in the same patient. PET/CT had been normalized following ABVD × 6. Three months after the completion of involved field radiotherapy the patient presented with lumbar pain and elevated ESR and C-Reactive Protein levels. MRI revealed osseous abnormalities, which were confirmed by PET/CT. PET/CT normalized again after IGEV salvage chemotherapy and BEAM with autologous stem cell support

Finally, baseline PET/CT may be used to determine the metabolic tumor volume (MTV), which is a combined evaluation of both tumor burden and metabolic activity. Preliminary results suggest that higher MTV may be independently associated with the outcome in HL and DLBCL, but this needs further evaluation before the introduction in clinical use [8, 9].

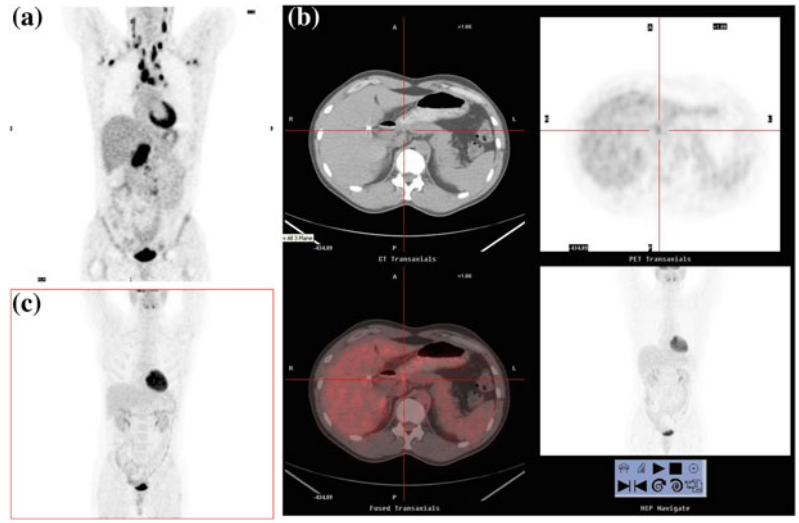

Fig. 35.4 **a** Baseline staging in a patient with Hodgkin lymphoma. The patient had disseminated nodal disease, including a mass at the hepatogastric junction, and a positive bone marrow biopsy (stage IVB). **b** Interim PET after two cycles of ABVD revealed complete resolution of FDG uptake except of the hepatogastric mass, which was reduced in size and had residual FDG uptake just above that of the liver. Interim PET was interpreted as positive, Deauville score 4. The patient received intensified chemotherapy with six cycles of BEACOPP-escalated. **c** Negative end-of-treatment PET in the same patient. He remains in complete remission 3 years after the positive interim PET/CT (Courtesy of Drs Datseris I and Rondogianni Ph, Department of Nuclear Medicine and PET/CT, Evangelismos General Hospital, Athens, Greece).

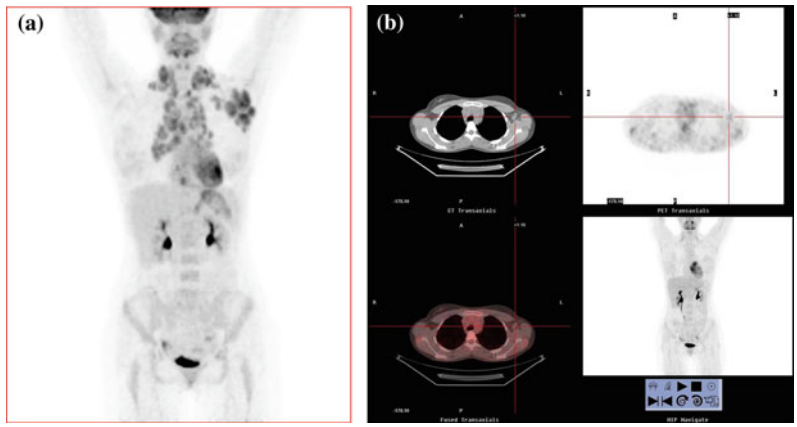

Fig. 35.5 **a** Baseline staging in a patient with Hodgkin lymphoma demonstrating stage IIB disease with extensive supradiaphragmatic nodal involvement. **b** Interim PET revealed a residual left axillary abnormality with FDG uptake above the surrounding background but below the mediastinal blood pool. Interim PET was interpreted as negative, Deauville score 2. The patient continued on ABVD. Posttreatment PET/CT was negative. Following involved field radiotherapy, the patient remains in complete remission 30 months after the negative interim PET/CT (Courtesy of Drs Datseris I and Rondogianni Ph, Department of Nuclear Medicine and PET/CT, Evangelismos General Hospital, Athens, Greece).

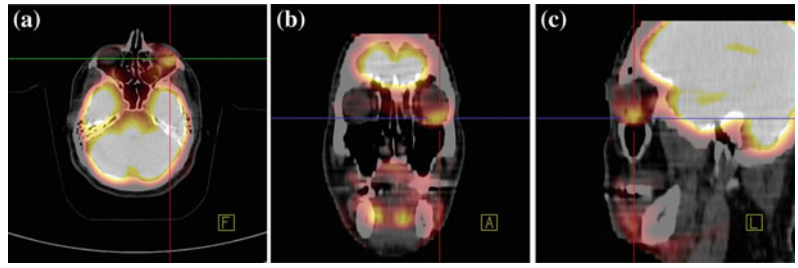

Fig. 35.6 Extranodal marginal zone lymphoma of the *left* eye. A mass with increased FDG uptake is shown. Marginal zone lymphomas are not routinely FDG-avid. According to current guidelines, PET/CT is not recommended either for baseline staging or for posttreatment evaluation in this entity

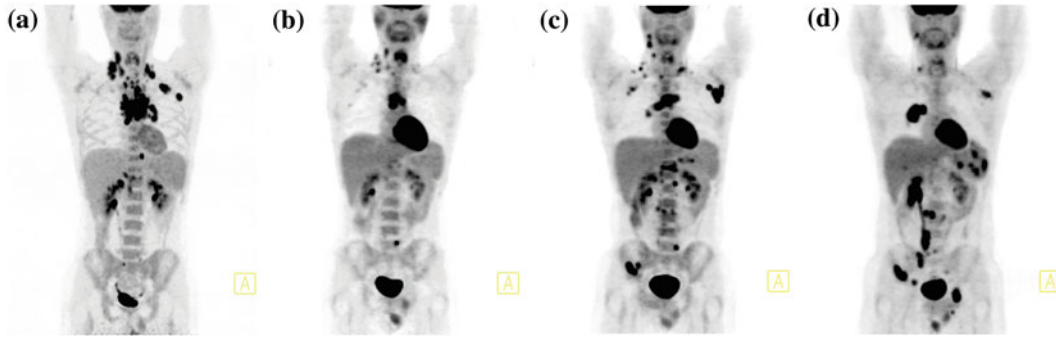

Fig. 35.7 **a** Baseline staging in a patient with Hodgkin lymphoma: Extensive supradiaphragmatic as well as infradiaphragmatic involvement consistent with stage IIIB disease. **b** Interim PET after two cycles of ABVD revealed persistence of multiple nodal sites on both sides of the diaphragm with FDG uptake markedly greater than that of the liver. A new focal osseous lesion is also seen. Interim PET was interpreted as positive, Deauville score 5. The patient continued on ABVD. **c** End-of-treatment PET after a total of six ABVD cycles demonstrated further progression. The patient had progressive disease by conventional restaging as well. **d** Further progression later on, during disease course in the same patient. Multiple focal splenic lesions are noted

35.2.3 PET in the Assessment of Bone Marrow Involvement

Several studies have investigated the role of PET in the identification of bone marrow involvement . In a meta-analysis including 587 lymphoma patients the reported sensitivity and specificity of PET against bone marrow biopsy was 51 and 91 %, which became 54 and 92 % if patients who were re-biopsied were included [10]. The comparative accuracy of PET/CT and bone marrow biopsy is highly depended on the specific lymphoma histologic type under evaluation.

In a recent large study, 454 HL patients were staged by both PET/CT and bone marrow biopsy [11] (Fig. 35.4a). As expected [12], 6 % (27 patients) had bone marrow involvement. However, 13 % (59 patients) had multi- ($n = 31$), bi- ($n = 9$), or unifocal ($n = 19$) PET/CT bone lesions and a negative bone marrow biopsy. Among 27 patients with a positive bone marrow biopsy, 4 (15 %) had no evidence of bone/bone marrow disease in PET/CT, 21 (77 %) had multifocal lesions, 1 (4 %) had bifocal, and 1 (4 %) had unifocal lesions. No cases of bone marrow involvement were detected among patients with diffusely increased 18 FDG-uptake. These data suggest that the main PET/CT pattern associated with bone marrow involvement in HL is the presence of multifocal bone/bone marrow lesions. Thus, PET/CT revealed more than double the cases of bone marrow involvement than detected by unilateral

bone marrow biopsy alone. Patients with bone marrow involvement ($n = 27$) and those with multifocal PET/CT lesions ($n = 31$) had similar outcomes in terms of progression free survival (PFS). According to these data, the sensitivity of focal PET/CT lesions in predicting bone marrow disease, as reflected by bone marrow biopsy, is 85 and 86 %, while the positive and negative predictive value is 28 and 99 %, respectively. These results are similar to those reported in a relevant meta-analysis. However, when the gold standard for the detection of bone marrow disease was either focal PET/CT lesions or a positive biopsy, the sensitivity of PET/CT was 95 versus 31 % for bone marrow biopsy. According to the authors, bone marrow biopsy did not lead to treatment modification in any of the four patients with negative PET/CT findings, since all of them had already advanced disease (stage shift from III to IV). A recent study validated the above results and failed to identify any high-risk subgroup of patients, who might benefit from bone marrow biopsy in the absence of positive findings in PET/CT [13]. Bone marrow biopsy will probably be omitted in PET/CT-staged patients with HL in the near future [7]. Finally, PET/CT might facilitate the identification of foci of increased uptake in order to guide bone marrow biopsy, since bone marrow involvement can be patchy.

In DLBCL, the frequency of bone marrow involvement is 10–15 % (Fig. 35.2a). Bone marrow biopsy may be more informative, because more patients may have positive biopsies with negative PET/CT. Furthermore, in DLBCL, bone marrow involvement may be either concordant (large cell) or discordant (small cell) compared to lymph node histology [14]. This phenomenon, which is of prognostic significance, cannot be demonstrated by PET/CT. In a recent study of 89 patients with DLBCL, 7 were biopsy+/PET+, 7 were biopsy+/PET−, 10 were biopsy−/PET+ and 65 were negative by both methods [15]. Among the 10 biopsy−/PET+ patients, 9 had uni- or bifocal PET/CT findings and only 1 had more widespread findings. Among the 7 biopsy+/PET+ patients, 6 had multifocal or diffuse findings and 1 bifocal. A larger study has been reported in abstract form [16]: Among 374 patients with DLBCL, 95 (25 %) had bone marrow uptake; 18 % focal and 8 % diffuse. Only 16 patients (4.3 %) had a positive bone marrow biopsy in the presence of a negative PET/CT, but stage was already IV in half of them. Thus the authors proposed that PET/CT might replace biopsy in DLBCL, since upstaging to stage IV was missed in only 8/374 patients (2.1 %). These data deserve further verification with detailed PET findings and precise bone marrow histology reported. Similar findings were recently reported by other investigators as well [17,18].

In indolent lymphomas bone marrow biopsy is the gold standard for the evaluation of bone marrow disease, which is much more prevalent than in HL and DLBCL. PET/CT may not reveal bone marrow involvement by low-grade lymphoma [2]. Whatever the case, PET/CT is not currently considered mandatory for baseline staging of indolent lymphomas.

35.3 PET/CT in Response Assessment After Completion of Therapy

35.3.1 Criteria for Response Assessment and Definitions of PET Positivity

Response assessment has been traditionally based on the International Working Group Criteria described by Cheson et al., which were updated in 2007 in order to include PET findings, where appropriate [6]. The revised response criteria are summarized in Table 35.1 (Figs. 35.1b, 35.2c, 35.4c, 35.5c).

The most important information provided by PET, as far as response evaluation is concerned, is the differentiation between viable lymphomatous tissue and necrotic or fibrotic tissue at residual masses apparent on CT. Furthermore, PET/CT may uncover occult disease in normal-sized lymph nodes or bone marrow disease,

Table 35.1 Revised response criteria for malignant lymphoma in the PET era (adopted with modifications from Cheson et al. [6])

Complete remission (requires all of the following)
1. *Clinical findings*. Complete disappearance of all clinical evidence of disease and disease-related symptoms, if present at baseline
2. *Nodal disease*
• *Typically FDG-avid lymphoma or baseline PET positive:* PET negative. Residual mass of any size is permitted provided that PET is negative
• *Variably FDG-avid lymphoma or baseline PET negative:* Regression of all lymph nodes to normal size, i.e.: (a) ≤1.5 cm in greatest transverse diameter if it were >1.5 cm before therapy or (b) ≤1 cm in short axis, if 1.1–1.5 cm in long axis and >1 cm in short axis before treatment
3. *Splenic and liver disease*. Non-palpable organs and normal sized (if considered enlarged before treatment) and/or disappearance of nodules. However, splenic involvement cannot be reliably assessed based on its size
4. *Bone marrow*. No infiltration on repeat bone marrow biopsy of adequate size (preferably >2 cm). If morphology is indeterminate, immunohistochemistry should be negative
Partial remission (requires all of the following)
1. *Nodal disease*
• *Typically FDG-avid lymphoma or baseline PET positive:* Regression on CT (as described above and below for variably FDG-avid lymphoma), but at least one previously involved site PET positive (applicable to non-nodal disease as well)
• *Variably FDG-avid lymphoma or baseline PET negative:* ≥50 % decrease in the sum of the products (SPD) of up to six of the dominant nodes or masses and no increase in other nodes (dominant sites selected based on the following criteria: clearly measurable in at least two perpendicular dimensions, located at disparate body regions if possible, including mediastinal and retroperitoneal nodes if involved).
2. *Splenic and liver disease*. ≥50 % decrease in the SPD of nodules. In case of single nodule, ≥50 % decrease in its greatest transverse diameter. No increase in spleen or liver size
3. *Bone marrow*. Irrelevant if previously positive. Persistent bone marrow disease is classified as PR, if CR criteria are otherwise fulfilled. Clinical CR without bone marrow assessment in patients with baseline positive bone marrow is also classified as PR
Stable disease
1. *Failure to attain the criteria for CR/PR but not fulfilling the criteria of relapse/progression (see below)*:
• *Typically FDG-avid lymphoma or baseline PET positive:* PET should be positive at prior sites of disease without new areas of involvement in posttreatment CT or PET
• *Variably FDG-avid lymphoma or baseline PET negative:* No change in the size of previous lesions on the posttreatment CT scan
Relapsed/progressive disease (requires at least one of 1–3)
1. Appearance of any new lesion >1.5 cm in any axis during or at the end of therapy (even if other lesions are decreasing in size)
• Increased FDG uptake in a previously uninvolved site should be confirmed by other modalities in order to be considered as relapsed/progressive disease
• New lung nodules are mostly benign in the absence of prior history of pulmonary lymphoma. Therapeutic decisions should not be made solely on the basis of PET without histologic confirmation in such cases
2. ≥50 % increase from nadir in the SPD of any previously involved nodes, or in a single involved node or the size of other lesions (splenic or hepatic nodules). A node with a short axis of <1 cm should increase by ≥50 % and to a size 1.5 × 1.5 cm or >1.5 cm in the long axis
3. ≥50 % increase in the longest diameter of any single previously identified node >1 cm in short axis
4. Lesions should be PET-positive, if observed in a typical FDG-avid lymphoma or the lesion was PET-positive before therapy (unless the lesion is too small to be detected with current PET systems (long axis <1.5 cm by CT)

which may not be demonstrable by trephine biopsy. In 2005, Juweid et al. published a retrospective study in patients with aggressive NHL, predominantly DLBCL, who underwent PET and CT after 4–8 cycles of chemotherapy [15]. They noticed that patients otherwise categorized as CRu (Complete Response Unconfirmed) based on Cheson's 1999 criteria of response, were usually PET-negative, and, overall, had a favorable outcome with PFS similar to that of the CR group. Patients in PR had strikingly different outcomes when PET was negative or positive. Moreover, incorporation of PET in IWC (International Workshop Criteria) was reported as an independent prognostic factor for PFS [19].

Small studies and systematic reviews [20, 21] demonstrated and confirmed the high negative predictive value of PET for final response assessment. Based on such data, PET was incorporated in the revised criteria for assessment of response to therapy in malignant lymphoma in 2007 in the context of the International Harmonization Project (IHP) [6, 22], in which the CRu category was eliminated and PET-negativity is compatible with CR irrespectively of the conventional radiographic response status.

The definition of PET/CT positivity is an important issue. Final (end-of-treatment) response assessment criteria differ from those used for interim (mid-treatment) evaluation. Specific guidelines for final response assessment have been published in the context of the International Harmonization Project [22]. These data are summarized in Table 35.2 (Figs. 35.1b, 35.2c, 35.4c, 35.5c, 35.7c).

Table 35.2 Guidelines for the interpretation of end-of-treatment PET-scans in patients with malignant lymphomas (Modified from Juweid ME et al. J Clin Oncol. 2007; 25:571–578, [22])

(1) Visual assessment only (and not semi-quantitative or quantitative estimations, such as SUVmax) is required to determine if PET is positive after the end of treatment
(2) Based on visual assessment, a positive PET is defined as focal or diffuse FDG uptake above the background in a location, which is not compatible with normal anatomy/physiology, with the following exceptions
a. *If the residual mass is* ≥*2* cm (regardless of its location), PET is defined as positive only if FDG uptake exceeds that of the mediastinal blood pool structures. Mild and diffuse uptake (between the background and the mediastinal blood pool structures) is considered negative for lymphoma. In contrast, smaller residual masses (<2 cm) or normal sized nodes are considered positive if their uptake exceeds the surrounding background, due to the effect of partial volume averaging
b. *New lung nodules* ≥*1.5* cm—in the absence of baseline lung involvement—should be considered positive for lymphoma only if their FDG uptake exceeds that of the mediastinal blood pool structures. New lung nodules <1.5 cm may be PET-negative because of partial volume averaging effect; therefore active lymphoma cannot be excluded. However, new lung nodules in patients without baseline lung disease, who have achieved complete remission in all previously involved sites, should be considered negative (usually correspond to infectious or inflammatory changes)
c. *Residual splenic or hepatic lesions >1.5* cm are considered positive only if their uptake exceeds (or is equal to) that of the spleen or the liver respectively. *Smaller residual nodules (<1.5* cm*)* are considered positive, if their uptake exceeds that of the respective organ. *Diffusely increased splenic uptake* is considered positive, if exceeds that of the normal liver, unless cytokines have been recently administered
d. *Diffuse increase in bone marrow uptake* (even > liver) is usually due to post-treatment hyperplasia and should not be interpreted as lymphomatous infiltration. In contrast, *clearly increased (multi) focal bone or bone marrow uptake* is considered positive for lymphoma. Bone marrow biopsy should be repeated, if initially positive irrespective of PET result

35.3.2 Who Should Have PET-Based Response Assessment and When?

The use of PET/CT for final response assessment as well as accuracy parameters are highly depended on the histologic subtype of the lymphoma. PET/CT is routinely used for final response assessment in patients with HL and aggressive B-cell lymphomas. Its use in other FDG-avid subtypes is not recommended by current guidelines. However, FDG-avid T-cell lymphomas are usually restaged by PET/CT in everyday practice. In contrast, PET/CT restaging after immunochemotherapy may not be so informative in low-grade follicular lymphomas and MCL, since these diseases are incurable. In such cases, PET/CT is not generally recommended and should be preferably used within the context of clinical trials. When used in variably 18-FDG avid histologic subtypes, which is not also recommended as a general rule, it is essential to have a baseline PET/CT available in order to confirm that the tumor is 18-FDG avid (Fig. 35.6).

According to current guidelines, posttreatment PET/CT evaluation should preferably be performed 4–6 weeks (and at least 3 weeks) after chemotherapy and immunotherapy and 8–12 weeks after radiotherapy, in order to avoid false-positive findings due to inflammatory processes and false negative due to stunning from cytostatic drugs [6, 22]. As far as interim PET is concerned it should better be performed as close to the next chemotherapeutic cycle as possible (see next topic).

35.3.3 Clinical Data in Individual Lymphoma Subtypes

The positive and negative predictive values of post chemotherapy PET/CT depend on the histologic subtype (Hodgkin lymphoma vs. individual subtypes of non-Hodgkin lymphomas), the chemotherapy regimen applied, and the *a priori* probability of relapse, as reflected by clinical stage or even other prognostic factors.

Hodgkin Lymphoma

In patients with HL, a negative PET/CT after standard ABVD chemotherapy predicts a 5-year relapse free survival (RFS) of ~95 % in stages I/II (where ABVD is typically followed by radiotherapy) (Fig. 35.5) and ~80 % in stages III/IV (in which only few patients are irradiated) (Fig. 35.4c) [23]. These data may have important implications for the design of follow-up strategies. If advanced stage patients are treated with more aggressive chemotherapy such as BEACOPP-escalated, the 5-year RFS for patients with a residual mass of >2.5 cm and a negative post chemotherapy, PET/CT is approximately 90 % without radiotherapy [24]. In a large study, this was almost identical with the outcome of patients with CR or residual masses <2.5 cm, in whom PET/CT was not performed [24].

Despite additional radiotherapy, early stage patients who remain PET/CT positive after ABVD chemotherapy have a 5-year RFS of 40–65 % [25–27] (Fig. 35.1b). Higher 18-FDG uptake may be predictive of treatment failure in this setting and could have an impact on therapeutic strategies, but this needs further clarification [27]. In advanced stages, the figures are similar to early stages after ABVD, but it appears that, after more intensive chemotherapy such as BEACOPP-escalated, radiotherapy in >2.5 cm PET-positive residuals may be much more efficient for disease control with long-term RFS >80 % [24].

Primary Mediastinal Large B-cell Lymphoma

A negative PET/CT after R-CHOP is associated with >90 % cure rates in PMLBCL, even when radiotherapy is omitted in many patients [28–30]. If irradiated, PET/CT-positive residual masses are effectively controlled in ~70 % of cases [28–30] and the intensity of 18-FDG uptake may have a clinically meaningful prognostic role, since patients with higher uptake probably have significantly inferior outcomes [28,30]. These data need further verification,

because of the limited number of patients due to the rarity of the disease.

Diffuse Large B-cell Lymphoma

On the other hand, a negative PET/CT after R-CHOP carries a lower negative predictive value in DLBCL. The long-term event free survival (EFS) in these patients after a negative post R-chemotherapy PET/CT is 75–80 % and the probability of relapse may depend on their baseline relapse risk, as reflected by the International Prognostic Index (IPI), similarly to what observed in HL, as well as to the depth of conventional radiographic response (Fig. 35.2c). Patients with DLBCL who remain PET/CT-positive after R-CHOP have a <40 % probability to remain disease-free [31, 32]. Some data suggest that PET/CT-positive patients suitable for radiotherapy may enjoy prolonged remissions. This is mainly applicable to patients with isolated PET/CT-positive lesions [33].

35.3.4 Impact on Clinical Practice: Randomized Trials

Although the prognostic significance and the diagnostic accuracy of PET/CT have already been established, studies evaluating PET-guided treatment decisions are few. In a randomized trial, evaluating radiotherapy versus observation according to PET results in bulky HL patients (defined as masses ≥5 cm) who had >75 % disease regression and persistent residual masses after six cycles of VEBEP chemotherapy, the relapse rate was higher for the observation group (11/80 or 14 % vs. 2/80 or 2.5 %) [34]. Thus, for the time being, radiotherapy cannot be safely omitted in HL patients with bulky (or relatively bulky) disease who have adequate response to conventional chemotherapy but still have residual radiographic abnormalities. However, as already mentioned, radiotherapy can probably be spared irrespectively of the initial bulk in advanced HL patients with a negative PET and >2.5 cm residual abnormalities (and those with smaller or no abnormalities), if this response has been achieved with more intensive chemotherapy with BEACOPP-escalated or similar regimens, because ∼90 % of them remain disease-free at 5 years [24].

Finally, two recent randomized trials have focused to the possibility of omitting radiotherapy in early stage HL after a negative PET/CT following two or three cycles of ABVD. The design rather resembled an interim PET-, rather than an end-of-treatment-PET-driven trial and their preliminary results are interpreted as providing different messages [35, 36]: The preliminary results of the EORTC H10 trial have been recently reported and suggest that radiotherapy cannot be safely spared in patients with stage I/II HL, who become PET/CT-negative after two cycles of ABVD: Patients who became PET/CT-negative after ABVDx2 were randomized to receive: (1) one or two further ABVD cycles (according to the absence or presence of risk factors) plus 30 Gy involved node radiotherapy (standard arm) or (2) two or four further ABVD cycles (according to the absence or presence of risk factors) without radiotherapy (experimental arm). The study was prematurely terminated due to excess relapses in the no-radiotherapy arms [35]. In contrast, the British RAPID trial preliminarily suggested that radiotherapy could be spared in patients with clinical stage IA/IIA HL and no mediastinal bulk (<0.33 at T5/6) who become PET/CT-negative after three cycles of ABVD [36]: Patients who became PET/CT-negative 10–12 days after day 15 of the third ABVD cycle (Deauville categories 1 and 2; Table 35.3), were randomized to receive involved field radiotherapy or no further treatment. The 3-year PFS was 93.8 versus 90.7 % for irradiated versus non-irradiated patients. The difference was −2.9 % with 95 % confidence intervals, -10.7 to +1.4 % (the study allowed for a noninferiority margin of −7.0 %). However, the difference was greater in an "as treated" analysis, since a fraction of patients randomized to receive radiotherapy was not actually irradiated [37]. Further follow-up is obviously needed before concluding that omission of radiotherapy is feasible, although the difference between the two arms appears to be

Table 35.3 Five-point scale for the evaluation of interim PET/CT-scan in patients with malignant lymphomas (Deauville criteria). Interim PET-scans graded as 1, 2, or 3 are considered negative. Grades 4 and 5 define positive interim PET-scans

1.	No abnormal FDG uptake
2.	FDG uptake ≤ mediastinum
3.	Mediastinum < FDG uptake ≤ liver
4.	FDG uptake moderately increased above the liver at any site
5.	FDG uptake markedly increased above the liver at any site and/or new sites of disease

small. Other randomized trials assessing similar questions as well as the impact of treatment intensification in PET/CT-positive patients are in progress.

35.4 Interim Response Assessment

Early prediction of response to therapy is of major importance, not only for prognostic reasons, but also as a potential basis for early treatment modification. CT, providing anatomic assessment, faces certain limitations, especially when bulky disease is present. Functional changes that precede anatomic ones could potentially be more accurate in predicting treatment response early in the course of therapy.

35.4.1 Who Might Benefit from Interim PET-Based Early Response Assessment?

Early response assessment has provided a major prognostic clue for patients with advanced Hodgkin lymphoma [38, 39]. The prognostic effect of interim PET is less marked, but still significant, for patients with diffuse large B-cell lymphoma. In the specific setting of primary mediastinal large B-cell lymphoma, interim PET does not appear to have an impact on the outcome [40]. Data on other lymphoma subtypes are sparse. However, the use of interim PET is not still recommended to guide treatment decisions.

35.4.2 Clinical Data in Individual Lymphoma Subtypes

Hodgkin Lymphoma

In HL, interim PET/CT positivity is evaluated according to the recently established Deauville criteria (Table 35.3). A negative interim PET/CT may not be nominally negative: Any positivity in previously involved sites with 18-FDG uptake up to that of the liver is acceptable as a favorable interim response (Deauville scores 1, 2, 3) (Fig. 35.5b). Any uptake higher than the liver is considered positive (scores 4, 5) (Figs. 35.4b, 35.7b). Using the criteria established in Deauville, the International Validation Study demonstrated that the 3-year PFS for patients with negative and positive interim PET/CT was 95 versus 28 % [41]. Such figures may apply not only to advanced HL, but also to intermediate stage HL (localized stages with ≥1 unfavorable features). However, the outcome of interim PET/CT-positive patients with localized disease and no adverse factors, especially no bulky disease, may be much better than the ~30 % reported above [26, 38, 42]. For the time being, the use of interim PET/CT is not recommended outside the setting of clinical trials. On the other hand, there are interesting data indicating that treatment intensification with BEACOPP-escalated in patients with advanced or even intermediate stage HL, who remain PET/CT-positive after two ABVD cycles, may produce long-term PFS rates of ~65 % (vs. ~30 % expected based on historical data) [43,44] (Fig. 35.4b).

Under BEACOPP-escalated, the negative predictive value of interim PET/CT is also >90 %; nevertheless, the positive predictive value is much lower compared with ABVD-treated patients, since the long-term PFS of interim PET/CT-positive patients may be up to 50–60 % [45].

Although major studies agree in that the negative predictive value of interim PET is at least 90 % irrespective of the chemotherapy regimen used, other series revealed less

impressive values (for example, 80-85 % or even less) [44, 46, 47]. Whether the a priori risk of failure as reflected by stage IV or other prognostic factors may affect the negative predictive value of interim PET should be further investigated [39, 44, 47, 48].

Diffuse Large B-cell Lymphoma

In DLBCL, interim PET/CT is also predictive of the outcome after R-CHOP or similar immunochemotherapy, but differences are not so marked compared with HL. Deauville criteria are not so widely accepted in this setting, because of their moderate reproducibility and prognostic capacity [49, 50] (Fig. 35.2b). Alternatively, a satisfactory interim PET/CT response can be defined by a >66 % reduction in SUVmax between baseline and interim assessment. In the NHL International Validation Study , based on 120 DLBCL patients treated with standard R-CHOP-21 or intensified R-CHOP-14 or R-ACVBP-14, where no PET-driven treatment modification was made, the 2-year EFS was approximately 80 versus 41 % in patients with >66 and ≤66 % SUVmax reductions after two cycles of immunochemotherapy, while 2-year PFS was 83 versus 54 % [50]. In the LNH-2007 3B trial, higher risk, young DLBCL patients were randomly assigned to receive either R-CHOP-14 or R-ACVBP-14, and underwent interim PET assessments after two and four cycles, which modified subsequent treatment strategy. The study confirmed that visual analysis was not accurate enough. The cutoff for SUVmax reduction was set at 66 % for PET-2 and 70 % for PET-4. The 2-year PFS according to PET-2 was 77 versus 57 %, while it was 83 versus 40 % according to PET-4 [51]. Clinical trials are currently examining the potential role of treatment intensification in interim PET/CT-positive patients with DLBCL [52]. In the PETAL trial, preliminary results revealed a sixfold higher relapse rate in patients with aggressive NHL, mostly DLBCL, who had not achieved a 66 % SUVmax reduction after two cycles of R-CHOP as compared to those who had, despite treatment intensification with a protocol designed for Burkitt lymphoma in patients randomized to the experimental arm [52]. Such strategies are not justified outside the investigational setting for the time being.

Issues on Reproducibility of Interim PET Reading

The reproducibility of various criteria for interim PET-based response assessment is a major issue, which should be addressed before such strategies become widely adopted. Furthermore, when studies are evaluated—especially the initially published ones—the reader should take into account the definition of interim PET positivity used in each study, which may affect the magnitude of the difference in PFS between negative and positive cases [38, 39, 48, 53, 54].

In HL, the International Validation Study suggested that the concordance (paired among 6 reviewers) regarding whether interim PET was negative or positive (visual analysis, Deauville score 1, 2 or 3 vs. 4 or 5) ranged from substantial to almost perfect (Cohen's K 0.70–0.84). The impact of interim PET on PFS was much stronger if PET was centrally reviewed than after local interpretation. However, in DLBCL, both ECOG (Eastern Cooperative Oncology Group) and Deauville criteria display only moderate reproducibility among independent reviewers [49]. In the NHL International Validation Study, the concordance among three reviewers regarding whether interim PET was negative or positive (visual analysis, Deauville criteria) was substantial ($K = 0.65$) if liver was used as reference (Deauville 4,5 positive), or even moderate ($K = 0.49$), if reference was the mediastinal blood pool (Deauville 3, 4, 5 positive). However, if SUVmax-based assessment with a 66 % cutoff was used, concordance was upgraded to almost perfect ($K = 0.81$).

35.5 PET in Autologous Stem Cell Transplantation

The evaluation of PET in patients with lymphoma undergoing Autologous Stem Cell Transplantation (ASCT) was introduced early in the course of utilization of PET in clinical practice. Generally, published studies have included mixed (HL and NHL) patient populations: Patients with positive pre-transplant PET have inferior outcomes than those with negative studies. Pre-transplant PET appears to be an independent predictor from established clinical risk scores at the time of relapse/progression [55]. In a meta-analysis of 12 studies, incorporating 630 patients with HL and aggressive NHL who underwent ASCT and had been evaluated with pre high dose chemotherapy PET examination, Terasawa et al., reported a summary sensitivity of 69 %, summary specificity 81 %, similar prognostic accuracy among studies and shorter PFS for patients with positive PET-scan [56]. Another meta-analysis reported hazard ratios of 3.2 (for disease progression) and 4.5 (for death) for patients with positive versus negative pre-transplant PET [57].

In relapsed/refractory Hodgkin lymphoma, patients who become PET-negative with salvage chemotherapy and undergo ASCT have a long-term remission rate of 80–85 % versus 40–50 % for those who remain PET-positive [58, 59] (Fig. 35.8). These results demonstrate that failure to achieve a PET-negative status does not preclude ASCT in patients with HL, especially if they are chemosensitive by conventional imaging [58]. However, more standardized protocols are required for evaluation of pre-transplant PET/CT in patients undergoing ASCT: It is not clear whether pre-transplant PET should be evaluated under the rules of interim or end-of-treatment PET or even if SUVmax-based criteria should be implemented. As a general rule, the decision to proceed to ASCT in relapsed/refractory Hodgkin lymphoma should be based rather on conventional chemosensitivity criteria than on PET evaluation.

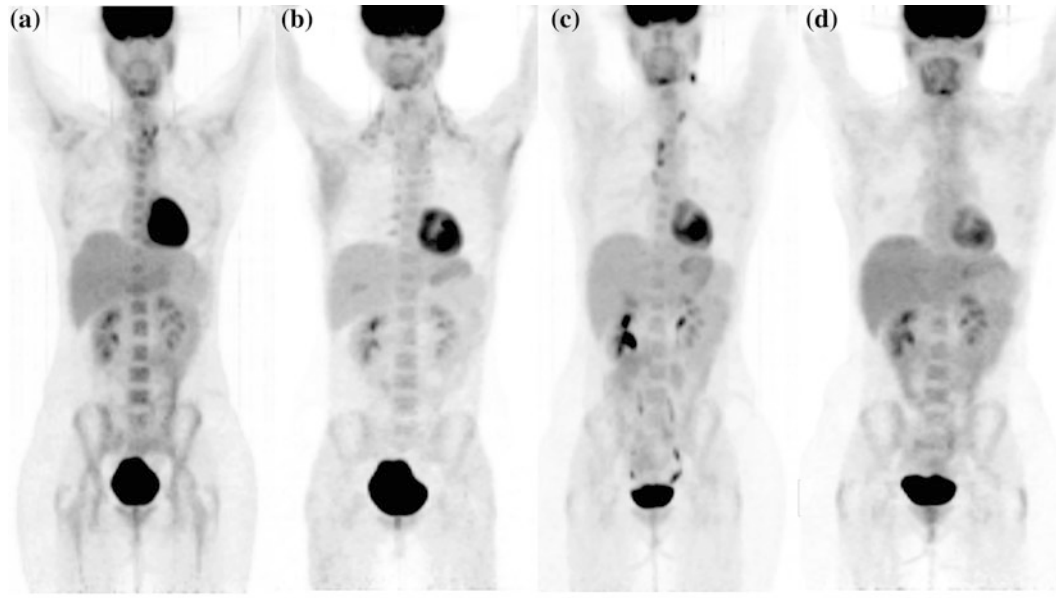

Fig. 35.8 **a** 18 FDG-PET before autologous transplantation in a patient with relapsed Hodgkin lymphoma: hypermetabolic lymph nodes at the upper mediastinum. **b** 18 FDG-PET 4 weeks after autologous transplantation: negative. **c** Relapsing disease 6 months later. **d** The patient received additional radiation treatment and reached CR (PET negative)

35.6 The Role of PET/CT in the Follow-up of Lymphomas

Once a negative PET/CT has been achieved, routine follow-up of patients with HL and aggressive B-cell lymphomas with PET/CT is not recommended, because the risk of false-positive findings outweighs any potential benefit of "earlier" identification of relapse and will lead to many unnecessary invasive procedures to exclude relapses. There is also no role for PET/CT in the follow-up of other lymphoma subtypes.

PET/CT is not a standard restaging procedure for relapsing lymphoma (Fig. 35.3b), but it may have a role in patients, mainly those with HL, who could be candidates for local treatment with curative intent.

35.7 Conclusions

FDG-PET is a unique equipment in the hands of hematologists, with high prognostic significance and accuracy, which has altered the definitions response to treatment and has already a major impact on the design of treatment and follow-up strategies. However, its exact role in guiding treatment decisions needs to be defined by randomized trials, many of which are ongoing. Questions under investigation include the role of PET to decide which patients should be irradiated, the potential of improving outcomes by early treatment intensification in interim PET-positive patients, or conversely, the possibility of treatment reduction in patients with negative interim PET. Evidence-based data on the appropriate use of PET in lymphomas are expected to be available shortly.

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